

# Typhoid Fever

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## KEYWORDS:

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Salmonella paratyphi

A 26-year-old presented to the ER with symptoms of unknown infection. Upon admission and hospitalization, the patient's vitals, labs, and hemodynamic function decreased; therefore, he was placed in the ICU for further management. After blood cultures came back positive for Salmonella typhi, the patient was started on strong antibiotics and eventually stabilized and was released home. This case represents an atypical presentation and the further management of Salmonella typhi infection in the primary care setting.

The patient presented to the emergency room as a recent traveler to America from India, where Salmonella typhi is considered endemic. A few hours from initial presentation, the patient deteriorated and was admitted to the ICU, where further workup was done, including imaging, cultures, and labs. After blood cultures came up positive for non-lactose fermenting gram-negative rods, later identified to be the Salmonella typhi organism, the patient was put on tobramycin and levofloxacin for 10 days; he eventually stabilized and was discharged home.

Primary care physicians see everything from standard follow-up for hypertension to acute and/or chronic exacerbations of heart failure. It is vital that the physician is prepared for anything that accompanies a patient through the door. The case represented below indicates that, for primary care physicians in ambulatory, urgent care, emergency and inpatient settings, typhoid fever should be considered in the differential diagnosis for patients with a history including recent travel to or from endemic areas, as the early diagnosis of typhoid fever could be the difference between life and death for the person infected.

## INTRODUCTION

Typhoid fever is a life-threatening condition caused by the bacterium Salmonella typhi. The illness is usually contracted by eating contaminated foods. The bacterium spreads via absorption and translocation through the intestinal mucosa into the bloodstream. The bacteria can be found in food and drinks handled by someone who is infected with the illness, or in sewage contaminated by the bacteria. Most cases are seen in developing nations where sanitation protocols for food preparation may be absent or insufficient.<sup>1</sup>

Typhoid fever affects approximately 22 million people annually.<sup>2</sup> Most cases reported in the United States are from patients who had recent traveled to endemic areas. There are approximately 200-300 reported cases in the United States annually.<sup>6</sup>

Bacteria can infect multiple organs via hematogenous spread including, but not limited to, the liver, spleen, and lymph nodes. Symptoms include fever, headache, malaise, abdominal

pain, and rash. Complications can include septic shock, acute colitis with intestinal perforation and acute peritonitis, renal failure, and death.<sup>4</sup> Diagnostic workup includes a complete blood count which may show leukocytosis with bandemia and thrombocytopenia, blood cultures, stool cultures, ELISA urine assay, and fluorescent antibody studies.

First line treatment of choice depending on resistance patterns, age of patient, and other factors include third generation cephalosporin, fluoroquinolones, or azithromycin.<sup>10</sup> There are widespread, multi-drug resistant strains to ampicillin, chloramphenicol, and trimethoprim-sulfamethazole in endemic areas of Asia. Public Health officers and the World Health Organization is monitoring for resistance to the fluoroquinolones and cephalosporins.<sup>2</sup>

Education about hygiene practices in food preparation, clean water sources and vaccinations are the mainstay of prevention. Ty21a is the live attenuated oral vaccine which is based on the Vi antigen of the microorganism. The vaccine is available as enteric capsules and available for use in children as young as 2 years of age. It has been shown to be safe and immunogenic, and offer protection to those that are unvaccinated.<sup>2</sup> Currently, the vaccination is available in the United States and other developed nations. The other vaccination is a capsular polysaccharide Vi vaccination that has shown positive results in endemic areas.

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Further emphasis in providing this resource to developing nations, where there is the greatest need, is essential.<sup>10</sup>

## CASE REPORT

We report on a 26-year-old otherwise healthy male, originally from India, who became infected with *Salmonella typhi* during a visit to the United States. Upon presentation to the Emergency Department he reported nausea, vomiting, and upper abdominal pain for the past 5 days. He also reported two days of fever (105.4°F) and chills.

Prior to his arrival in the United States he denied any such gastrointestinal problems. He indicated that within 24 hours of eating at a fast food restaurant with friends, he experienced a transient gastrointestinal disturbance consisting of nausea, vomiting, and diarrhea, all of which appeared self-limiting.

Subjective history and review of symptoms were otherwise unrevealing. Physical examination was unremarkable except for conjunctival icterus. Over a time period of a few hours after presentation the patient began experiencing rapidly decreasing blood pressure, hyponatremia, hypocarbia, as well as pancytopenia. Urinalysis revealed ketones, moderate protein, white and red blood cells (3/HPF and 6/HPF respectively). Within hours the patient was transferred from the general ward to the intensive care unit, due to hemodynamic instability. Medical management included inotropic and pressor agents support for several days, broad-spectrum antibiotic coverage including doxycycline, levofloxacin, and metronidazole, as well as a stress dose steroids. He responded well to this medical management, although the underlying etiology of his illness remained a mystery.

Further investigatory measures included sampling his blood and stool for *E. coli*, *Shigella*, *Campylobacter*, *Yersinia*, *S. aureus*, *Pseudomonas*, and yeast. This initial round of screening was all negative. Additionally, a chest x-ray was performed to rule out tuberculosis, and while no TB infection was noted, this study did reveal bibasilar pleural effusions. Abdominal CAT scan revealed mesenteric adenitis and bowel inflammatory processes. Meanwhile, the patient continued to spike fevers and experience tranaminitis, with both alanine and aspartate aminotransferase levels above 200. Two consecutive sets of blood cultures eventually revealed non-lactose fermenting gram-negative rods; later identified as *Salmonella typhi*. After ten days of antimicrobial treatment with levofloxacin and tobramycin, the patient stabilized. He was discharged in stable condition with routine follow-up with his primary care provider upon returning to India.

## DISCUSSION

Family physicians are on the frontline for diagnosis and treatment of a number of illnesses. The recognition of certain

illnesses such as the one discussed above is vital to the survival of the patient that presents acutely ill.

Enteric fever is caused by *Salmonella typhi* and paratyphi. Although uncommon in the United States other than those acquired from travel abroad, typhoid fever is endemic and resistance to antimicrobials is increased in Africa, Asia, Central and South America as shown in Figure 1 among other places. The bacteria are transferred via the fecal-oral route by ingestion of contaminated water, food, or direct person to person contact.<sup>8</sup> Third world countries such as the areas mentioned above without proper sanitation of the food and water supply lead to the endemic nature of this illness. Groups in the United States and abroad that are especially susceptible to this illness are those that are immunocompromised such as those with sickle cell disease and HIV, in addition to recent travel to endemic areas.<sup>9</sup>

These patients can present to the ED, clinic, or urgent care with vague symptoms and abnormal presentation. The typical presentation of typhoid fever varies by the week of presentation.<sup>5</sup> Classically, the illness starts out acutely with headache, fever, abdominal pain, bradycardia, splenomegaly, and leukopenia.<sup>9</sup> Depending on the week, the patient can present to the healthcare setting with symptoms which can vary from high fever and constipation in the first week of infection to encephalopathy and intestinal perforation on the third

**Table 1: Frequency of Symptoms and Physical Findings in Patients with Enteric Fever**

Parameter	Typhoid Fever (%)	Paratyphoid A and B (%)
<b>Symptoms</b>		
Fever	39-100	92-100
Headache	43-90	60-100
Nausea	23-36	33-58
Vomiting	24-35	22-45
Abdominal cramps	8-52	29-92
Diarrhea	30-57	17-68
Constipation	10-79	2-29
Cough	11-86	10-68
<b>Physical findings</b>		
Fever	98-100	100
Abdominal tenderness	33-84	6-29
Splenomegaly	23-65	0-74
Hepatomegaly	15-52	16-32
Relative bradycardia	17-50	11-100
Rose spots	2-46	0-3
Rales or rhonchi	4-84	2-87
Epistaxis	1-21	2-13
Meningismus	1-12	0-3

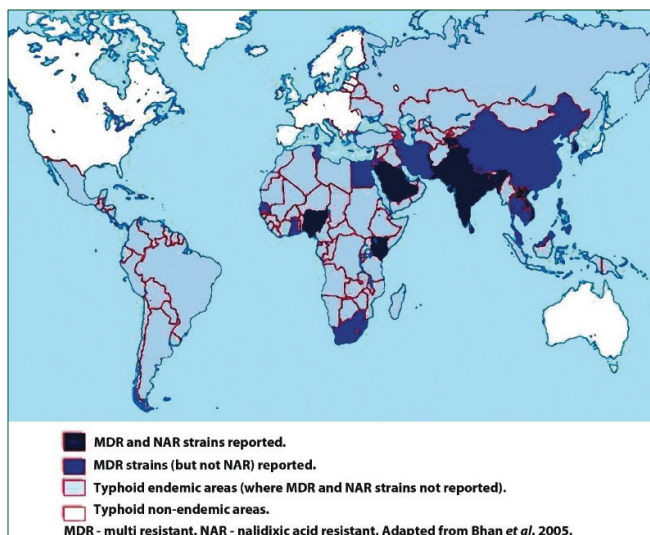


Figure 1 Global distribution of antimicrobial resistance in *Salmonella typhi* (1990–2004). Reproduced with permission from Bhan et al.

week.<sup>5</sup> The frequency of symptoms and physical exam findings can be seen in Table 1.<sup>9</sup> Compared to endemic countries the incidence of typhoid fever in the United States is minimal at only 200 to 300 cases per year. Interestingly, travelers to these endemic countries specifically Southeast Asia made up 80% of these reported cases.<sup>6</sup> Therefore, family physicians need to be aware of the different ways that the illness can present itself especially those that fall from the norm such as the one presented above. Other atypical presentations of typhoid fever range from acute gastroenteritis as the one above to burning micturition. In a study by Dutta et al, 32 adult patients were admitted to the hospital and 15 of those patients, or almost half of them, presented with atypical manifestations of typhoid fever. The symptoms that were observed on presentation included were the following: burning micturition with normal urine exam (15.6%), diarrhea in first week (6.2%), encephalopathy in first week (3.1%), isolated hepatomegaly (6.2%), bone marrow suppression (6.2%), and pneumonitis (3.1%). All of the patients with these symptoms were treated with proper antibiotics and response was favorable, and they were discharged home.<sup>7</sup> In addition to the symptoms that the patient presents to the clinic, physical exam and laboratory findings are very important to the diagnosis. These findings can narrow down the differential from the multitude of bacteria that mimic typhoid fever. Physical exam should be thorough and focus on the most common ways that the illness presents. Fever is present in 90% of cases. The fever is described as remittent and increasing in severity as the illness progresses. Relative bradycardia and the presence of rose spots or erythematous maculopapular lesions of 2 to 4 mm on the skin are helpful in confirming the diagnosis of typhoid fever as shown in figure 2. Some other physical exam findings that

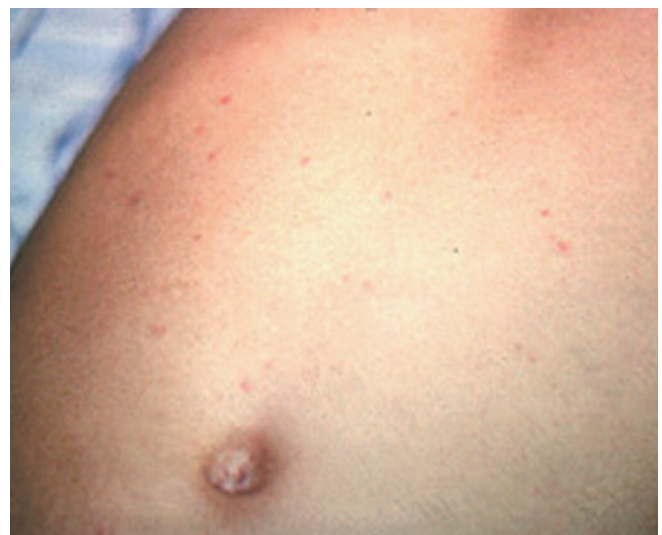


Figure 2 Typhoid rose spots. These are small, blanching maculopapular lesions, ~1-4mm in size, usually seen on the trunk. They may also take on a more purpuric, nonblanching character. Courtesy of CM Parry, Liverpool, UK.

can be seen with the illness are conjunctivitis in 44% of the patients, abdominal tenderness usually over the right lower quadrant, and splenomegaly. All these exam findings are good in narrowing down the differential diagnosis, but diagnosis is usually confirmed by lab findings.<sup>9</sup>

As soon as typhoid fever is suspected, and before empiric antibiotics are started, cultures from blood, bone marrow, or another sterile site need to be isolated for definitive diagnosis of *Salmonella typhi*. Multiple cultures from the blood that are positive for the organism increase the likelihood of a definitive diagnosis by 73% to 97%. In some cases, if rose spots are present on the patient these can also be cultured to confirm the diagnosis. This test is positive in 2/3 of patients with typhoid fever. In the past, the Widal test was used to detect *Salmonella typhi* antibodies and make a diagnosis of typhoid fever. This test has been shown to be positive in 46% to 94% of patients with typhoid fever, and unfortunately, false positives are common with this test especially in those with rheumatoid arthritis.<sup>9</sup>

Treatment of typhoid fever centers on antimicrobial therapy. Usually this therapy is started before the cultures confirm the diagnosis. Antibiotic treatment depends on the local resistance patterns, age of the patient, the setting, and what is available in the area. In the United States, treatment in adults starts with a fluoroquinolone such as ciprofloxacin at a dose of 500 mg twice daily or 400 mg of ofloxacin twice daily and for a duration of 7 to 10 days. If resistance is considered high in the area, these drugs should not be used as first line treatment. Other drugs that can be used if resistance is found are ceftriaxone at a dose of 2 to 3 g once daily parentally or cefixime at 20mg/kg per day divided twice daily for 7 to 14

**Table 2: Recommended antibiotic treatment for typhoid fever (adapted from WHO<sup>13</sup> and Bhutta<sup>12</sup>)**

Optimal Treatment				Alternative Effective Treatment		
Susceptibility	Drug	Daily dose (mg/kg)	Course (days)	Drug	Daily dose (mg/kg)	Course (days)
<b>Uncomplicated typhoid fever</b>						
Fully sensitive	Fluoroquinolone (such as Ofloxacin or Ciprofloxacin)	15	5-7	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8-40	14
Multidrug resistance	Fluoroquinolone or	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistance	Azithromycin	8-10	7	Cefixime	20	7-14
	Ceftriaxone	75	10-14			
<b>Severe typhoid fever requiring parenteral treatment</b>						
Fully sensitive	Fluoroquinolone (such as Ofloxacin)	15	10-10	Chloramphenicol	100	14-21
				Ampicillin	100	14
				TMP-SMX	8/40	14
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone or	60	
				Cefotaxime	80	10-14
Quinolone resistant	Ceftriaxone or	60	10-14	Fluoroquinolone	20	14
	Cefotaxime	80				

days. Azithromycin at 1 g oral dose once followed by 5-7 days of 500 mg once daily is another alternative. In children, the treatment is similar and includes one of the following: beta-lactam such as ceftriaxone 100 mg/kg per day via IV once daily for 10-14 days, a fluoroquinolone such as ciprofloxacin either orally or parenterally at a dose of 30 mg/kg daily for 7 to 10 days, or Azithromycin at 10 to 20 mg/kg once daily for 5 to 7 days.<sup>10</sup> The recommended antibiotic treatment of typhoid fever can be seen in table format in Table 2.<sup>12,13</sup>

Without proper treatment, complications do occur. Complications may develop in 10% of hospitalized patients. Figure 3 shows the amount of complications that can occur with typhoid fever. Some of the more serious complications include septic shock, ARDS, and gastrointestinal bleeding. Intestinal perforation after GI bleed and typhoid encephalopathy are some of the most common complications that due occur with typhoid fever. Perforation, the most serious complication, usually occurs at the terminal ileum and occurs in about 1-3% of hospitalized cases. Perforation can progress to shock and severe abdominal pain and requires emergent surgical intervention. The other complication associated with a high mortality rate is typhoid encephalopathy. This complication is associated with a mortality rate of up to 50% and can manifest as anything from agitation to delirium and coma. In patients with this presentation, cerebrospinal fluid needs to be obtained and other diagnosis need to be ruled out such as encephalitis and meningitis.<sup>8</sup> Chronic carriers can also

occur, and these patients will spread the bacteria in the stool for more than 12 months after initial infection. This occurs in 1-6% of those infected with *Salmonella typhi*. The patients themselves do not show signs of infection but in fact shed a large amount of the organisms in the stool. The biggest issue with chronic carriers is their presence in the field of food preparation. If these patients are in fact infected with the bacteria and not using proper sanitation techniques, they represent a significant infectious risk. Fluoroquinolones appear to be the most effective antibiotics used for treatment of those that are chronic carriers of *Salmonella typhi*.<sup>10</sup>

The role of prevention through proper water decontamination, good food hygiene, and other sanitation measures is the first step towards preventing spread of typhoid fever. Although this is not exactly possible for the primary care physician, primary care physicians can help through the use of vaccination of those that are at risk for typhoid fever. In the United States, vaccination should be directed at those that plan on traveling abroad to endemic areas such as southeast Asia.<sup>10</sup> There are two vaccines available at this time to prevent typhoid fever and its complications. One of the vaccinations is a parenteral Vi polysaccharide, and the other is the oral Ty21 vaccine.<sup>8,11</sup> The live oral Ty21 vaccination is available in the United States. It is administered in enteric-coated capsules or liquid formation. The vaccination is administered in four doses, two days apart and is indicated in adults and children 6 years of age and older. Booster doses are recommended every 5 years. Because the

vaccination is a live vaccine, it should be avoided in those that are immunocompromised or pregnant women. The other vaccination available is the capsular Vi vaccination. This is given as a single injection and is approved for those 2 years and older. Booster doses are recommended every three years. This vaccination has shown protective efficacy of 91.5% after 27 months in trials in Vietnam.<sup>10</sup> This inactivated vaccination should be given to patients at least two weeks before travel to allow the vaccination to work.<sup>11</sup>

Our case illustrates the importance of having a wide differential diagnosis with a patient who presents acutely ill. Without early detection and diagnosis of *Salmonella typhi*, our patient could have had complications from the illness including sepsis, intestinal perforation, and even death. Even though the patient was not the typical demographic of typhoid fever, he was from an area where typhoid fever is in fact endemic. Primary care physicians are the first line for diagnosis and treatment of these types of illness. Primary care physicians need to be aware of the risk factors of those that can present to the clinic with typhoid fever. Those people at risk include travelers to endemic areas, sickle cell disease patients, and others that are immunocompromised. In addition to diagnosis and treatment, it is important for the primary care physician to vaccinate those that may be travelling to these endemic areas described above in this report. If not vaccination, the primary care physician can also educate patients on careful observation of what they eat and drink while traveling abroad and possible signs and symptoms of the endemic infection. Typhoid fever must be in the differential diagnosis for those that present to the primary care physician acutely ill especially in those that recently traveled abroad to endemic areas.

### Figure 3: Important complications of typhoid fever

#### Abdominal complications

- Gastrointestinal bleeding
- Intestinal perforation and shock
- Hepatitis with/without jaundice
- Cholecystitis

#### Genitourinary complications

- Retention of urine
- Glomerulonephritis

#### Cardiovascular complications

- Asymptomatic ECG changes
- Myocarditis
- Sudden death

#### Respiratory complications

- Pneumonia
- Bronchitis

#### Hematologic complications

- Anemia
- Disseminated intravascular coagulation (DIC)

#### Focal infections

- Abscesses of brain, liver, spleen etc.

#### Neuropsychiatric complications

- Encephalopathy – reduced consciousness levels
- Meningitis
- Seizures

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